REMARKS

Claims 1-10, 12-13, 23-28, 31, 34-35, 55-64, 69-70, and 72 have been withdrawn. Claims 30, 33, and 36 are cancelled herein and claims 11, 29, and 32 have been amended without prejudice to, or disclaimer of, the subject matter therein. Applicants reserve the right to pursue the cancelled subject matter by way of continuing or divisional applications. Support for the amended claims may be found in the original claims and throughout the specification. Thus, no new matter has been added. Claims 1-13, 23-29, 31-32, 34-35, 53-66, 69-70 and 72 are pending in the current application.

Election/Restrictions

The Examiner has made the restriction requirement FINAL.

The Rejections Under 35 U.S.C. § 112, 1st ¶, Written Description, Should be Withdrawn

Claims 65-66 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. This rejection is respectfully traversed.

The rejection states that the specification does not provide a written description for the genus of molecules recited in the claims. In particular, the rejection alleges that Applicants have not disclosed any immunoepitopes, nor which amino acid residues may be replaced without affecting immunogenicity. While this may be the appropriate legal standard for novel polypeptides, this is not the correct standard in the present case for reasons explained in the following paragraph.

Subsequent to the publication of the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001), the Federal Circuit clarified the written description standards applicable to the examination of subject matter in which a *known* composition is recited in the claims. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (CA FC 2003). The court explained that "[w]e held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself — not merely a recitation of its function or a reference to a

potential method for isolating it… …*Eli Lilly*…[is] inapposite to this case *because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend*." As in the *Amgen* appeal, Applicants are not claiming compositions made from new or unknown biological materials. Rather, the currently pending claims recite immunogenic compositions comprising a known polypeptide, namely BrkA (SEQ ID NO:34).

At the time of filing, the BrkA polypeptide had already been described in the scientific literature; much was known about its structure, including its sequence and structural regions. See Oliver *et al*. (2002) *Vaccine*, 20:235-41 (stating in the abstract that "BrkA is synthesised as a 103 kDa precursor that is processed in to a surface-associated N-terminal 73 kDa passenger domain, and an outer-membrane embedded C-terminal 30 kDa transporter moiety").

Further, the specification provides guidance regarding the epitopes of SEQ ID NO:34 on page 99, Table 5 (predicted B-cell epitopes) and Table 6 (predicted T-cell epitopes). These predicted epitopes are identified by position within SEQ ID NO:34. The specification contains further guidance regarding the length and structure of fragments comprising the predicted epitopes.

Applicants draw the examiner's attention to the new set of Written Description Training Materials published in 2008 which "supersede and replace the 1999 training materials," particularly Example 11. That example deals with a hypothetical situation in which there is an art-recognized structure-function correlation present, as here, and concludes that written description is satisfied.

Given the knowledge in the art of the structure of BrkA, including which portions are located on the surface and which are embedded in the membrane, as well as the guidance provided within the specification, the skilled person would easily comprehend the claimed subject matter. The written description standard is therefore satisfied. Applicants respectfully request that the rejection of claims 65-66 be withdrawn.

The Rejections Under 35 U.S.C. § 112, 1st ¶, Enablement, Should Be Withdrawn

Claims 65-66 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Applicants respectfully traverse.

The rejection takes the position that the person of skill in the art would not find it plausible that the composition would work absent in vivo proof of concept data showing a protective effect against infection. Thus, alleges the rejection, practicing the claimed subject matter would require undue experimentation. In making this allegation, the rejection equates the recitation of the term "vaccine" in the claims at issue with a requirement for protection against infection. Essentially, the Examiner alleges that Appellants' Examples do not provide sufficient correlation between the vaccine utility and the claimed composition.

The Manual of Patent Examination Procedure (MPEP) states:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision **based on finding that *in vitro* data did not support *in vivo* applications**).

Section 2164.02 (emphasis added).

At this point, Applicants note that claim 11, from which the rejected claims depend, has been amended to recite a composition comprising PT, FHA, and a polypeptide having 85% identity with SEQ ID NO:34 (BrkA).

The rejection acknowledges that the disclosure has provided in vivo murine data demonstrating that BrkA, in combination with pertussis toxin (PT) and FHA, (DTPa-2 BrkA) can produce statistically significant additional protection as compared to PT and FHA. See Example 12, cited on page 8 of the rejection. Although not

cited in the rejection, Example 13 also discloses that the protection conferred by DTPa-2 BrkA against *B. pertussis* strain 18323 was statistically equivalent to that provided by the DTPw (whole cell *B. pertussis*) and DTPa-3 (PT, FHA, and pertactin) vaccination. Despite this evidence, the rejection reasons that this "does not demonstrate that the composition confers 'protection against infection[,]'" but only that it "reduces infection." Here, the rejection has gone astray, because the evidence of record does establish a sufficient correlation to satisfy the appropriate enablement standard for the claims as amended.

It is widely acknowledged that current vaccines protect against severe disase, but do not eliminate *B. pertussis* from the body. See the first full paragraph, page 2 of the specification, citing Cherry *et al.* (1998) *Vaccine* 16:1901, among others. Indeed, the widely used vaccine comprised of PT, FHA, and pertactin provides only protection from the severity of whooping cough. See the last three lines of the paragraph spanning pages 1-2 of the specification. Thus, the skilled person would not expect a pertussis vaccine to confer protection from infection, only that it would reduce or protect against the severity of the infection. Evidence that a composition reduces infection sufficiently correlates the claimed composition with the recitation of the claim term "vaccine" for purposes of the enablement inquiry.

The rejection also cites Chandrashekar for the principle that the ability to stimulate antibody production does not necessarily correlate with the stimulation of a sufficient immune response and Ellis for the principle that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. However, as discussed above, the specification provides more than the demonstration of an antibody response and demonstrates an immune response in vivo that does confer protection statistically equivalent to that conferred by widely utilized vaccine compositions.

The rejection also cites Bowie small changes in amino acid sequence can abolish a polypeptide's natural biochemical activity or function. However, this is not relevant to the present enablement inquiry because the claims do not recite a biochemical activity.

The references cited in the rejection fail to establish that practicing the claims as amended would require undue experimentation. The concerns expressed by the rejection are therefore alleviated and the rejection should be withdrawn.

The Rejections Under 35 U.S.C. § 103, Should Be Withdrawn

Claims 11, 29-30, 32-33, 36, and 53-54 were rejected under 35 USC 103(a) as being unpatentable over Novotny *et al.* (US 7,479,283, 2009, date filed May 25, 1995) in view of Oliver *et al.* (*Vaccine* 20: 235-241, 2002) in further view of Kinnear *et al.* (*Infect. Immun* 69(4): 1983-1993, 2001). Applicants respectfully traverse.

Applicants note that claims 30, 33, and 36 have been cancelled, as described above.

The rejection asserts that Novotny differs from the claimed subject matter only in that it does not explicitly disclose the use of the BrkA in a vaccine formulation. The rejection then reasons that Oliver teaches that BrkA could be utilized in such a formulation and concludes that the combination would be obvious. Applicants disagree for the following reasons.

After carefully reviewing Novotny, Applicants representative notes that it teaches the following: "There is also provided a synergistic combination comprising i) the 69 kDa antigen from *B. pertussis* and ii) the filamentous haemagglutinin antigen of *B. pertussis* in an amount effective to induce protection in a mammal to subsequent challenge by a virulent strain of B. pertussis." Novotny actually teaches that the combination of the 69 kDa antigen and FHA is needed in order to achieve protection. Given the teaching of Novotny, the skilled person would not have a reasonable expectation of successfully producing a protective response using a formulation in which the 69 kDa antigen were absent. Thus, even if one combined the BrkA antigen of Oliver with the formulation of Novotny, the skilled person would not produce a composition in which the 69 kDa antigen were absent or only optionally present because there would be no reasonable expectation of success for such a composition. Thus, there is no motivation to produce such compositions.

In contrast, the amended claims recite compositions comprising a polypeptide sharing at least 85% identity with SEQ ID NO:34 (BrkA), FHA, and pertussis toxin. There is no requirement for the presence of the 69 kDa antigen.

It is elemental that a reference, or combination of references, must provide the skilled person with a reasonable expectation of successfully practicing the claimed invention in order to establish a prima facie case of obviousness under Section 103. Novotny does not establish a reasonable expectation of success for compositions that do not require the 69 kDa antigen and therefore fails to establish that such a composition is prima facie obvious. The rejection does not establish that either Oliver or Kinnear cure this defect. Accordingly, the rejection of claims 11, 29, 32, and 53-54 should be withdrawn.

CONCLUSION

Applicants submit that the amendments and comments discussed above have overcome the rejections under Section 112 and 103. Should any outstanding issues remain, the Examiner is encouraged to contact Applicants' undersigned representative.

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